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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,150	07/24/2006	Peter Herold	2006_0980A	4977

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EXAMINER	
MABRY, JOHN	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
12/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,150	HEROLD ET AL.	
	Examiner	Art Unit	
	JOHN MABRY	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment(s)

Applicant's response on September 12, 2008 filed in response to the Election/Restriction dated March 21, 2008 has been received and duly noted. The Examiner acknowledges Applicants' election of Group I with traverse.

Applicants' arguments were persuasive and the restriction requirement has been withdrawn. A second Non-Final Office Action is below.

Applicant's response on September 12, 2008 filed in response to the Office Action dated June 24, 2008 has been received and duly noted.

In view of this response, the status of the rejections/objections of record is as follows:

35 USC § 112 Rejection(s)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The 112-2nd rejection of claims 1-7 and 10-13 regarding the phrase "pharmaceutical preparation" have been overcome in view of Applicants amendment to the claim - deleting the phrase "preparation".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The 112-1st rejection of claims 1-7 and 10-13 regarding the term "prodrug" have been overcome in view of Applicants amendments to the claims.

Obviousness-Type Double Patenting Rejection(s)

The obviousness-type double patenting rejected has been withdrawn over US 2007/0021400 (11/488,860) in view of further reconsideration by Examiner.

The obviousness-type double patenting rejected has been withdrawn over US 2007/0021399 (11/488,858) is maintained. A further description of this rejection is described below. A properly executed Terminal Disclaimer is required to overcome rejection.

An action on the merits of claims 1-14 is contained herein below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "carbocyclic" is a relative term which renders the claim indefinite. The term "carbocyclic" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. This term could possibly be (a) saturated cycloalkyl structures i.e. cyclohexyl, (b) fully unsaturated cycloalkyl structures i.e. phenyl or (c) partially saturated cycloalkyl structures i.e. cyclohexene, cyclohexadiene. What does Applicant intend for this term to mean?

Claims 8-9 provides for the use of “use of a compound”, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 8-9 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

For examination purposes, the Examiner has interpreted and examined the “use” claims as a method of treating and/or preventing.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7 and 10-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for R1 and R2 being H, tetrahydropyranylalkylcarbonyl, piperidinyl alkylcarbonyl, alkylcarbonyl, phenyloxyalkylcarbonyl, acetyl, phenylalkanoyl, cyclohexylalkylsulfonyl, alkyl, cyclohexylcarbonyl, alkylaminoalkyl, imidazoylalkylphenyl, alkylaminecarbonyl, indenealkylcarbonyl, pyridinylalkylcarbonyl; R3 and R4 being H, alkoxycarbonyl; R5 being H; and R being phenyl substituted with alkoxyalkoxy, and H, but does not reasonably provide enablement for the entire scope as claimed for R1, R2, R3, R4, R5 and R and claimed substituents. Applicant is also not enabled for the term "optionally substituted" as claimed.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The Specification does not provide any support for said variables at R1, R2, R3, R4, R5 and R positions. The Specification describe starting materials and methods for synthesis of compounds wherein R1, R2, R3, R4, R5 and R are as mentioned above, but does not describe or list any reagents wherein compounds can be used to synthesis compounds where R1, R2, R3, R4, R5 and R are the entire scope as claimed.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims: Scope of the compounds. Owing to the range of many variables, millions of highly substituted amino alcohol compounds are embraced.

(2) The nature of the invention: The invention is a highly substituted amino alcohol compounds.

(3) Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and chemical reactivity (which is affected by determinants such as substituent effects, steric effects, bonding, molecular geometry, etc) is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(4) Direction or Guidance: That provided is very limited. Applicant shows a general synthesis of compounds of application's general formula I. The Specification describes starting materials and methods for synthesis of compounds wherein R1, R2, R3, R4, R5 and R are as mentioned above, but does not describe or list any reagents wherein compounds can be used to synthesis compounds where R1, R2, R3, R4, R5 and R are the entire scope as claimed. There is limited evidence in the Specification of the example compounds that only covers no or a small portion of the substituents claimed of formula. Thus, there is no specific direction or guidance regarding said compounds specifically mentioned in Scope.

For example, the specification does not provide any support for the synthesis of compounds, wherein R being carbocyclic or heterocyclic and its optional substituents. The specification defines the terms "carbocyclic" and "heterocyclic" as follows:

> Heterocyclyl bonded via a ring carbon or ring nitrogen atom contains generally from 4 to 8, in particular from 5 to 7, ring atoms, and may have 1 or 2 fused-on phenyl or cycloalkyl radicals, or else be present as a spiro compound. Examples include pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino, tetrahydrofuranyl, furanyl, pyranyl, tetrahydropyranyl, thiazolyl, oxazolyl, imidazolyl, indolinyl, isoindolinyl, 2,3-dihydrobenzimidazolyl, 1,2,3,4-
>
> tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydro-1,3-benzodiazinyl, 1,2,3,4-tetrahydro-1,4-benzodiazinyl, 3,4-dihydro-2H-1,4-benzoxazinyl, 3,4-dihydro-2H-1,4-benzothiazinyl, 3,4-dihydro-2H-1,3-benzothiazinyl, 3,4,5,6,7,8-hexahydro-2H-1,4-benzoxazinyl, 3,4,5,6,7,8-hexahydro-2H-1,4-benzothiazinyl, 2,3,4,5-tetrahydro-1H-1-benz[6,7-b]azepinyl and 5,6-dihydrophenanthridinyl. The radicals mentioned may be unsubstituted or N-substituted and/or C-substituted, in which case in particular 1, 2 or 3 substituents may be present.

The availability of the starting material that is needed to prepare the invention as claimed is at issue here…As per MPEP 2164.01 (b). A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to a make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court *in re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made it clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

It is not trivial to experimentally interchange any and all of the many substituents that exist. As generally described by F. Zaragoza Dörwald, most organic syntheses fail initially and chemical research is highly inefficient due to chemists spending most of their time "finding out what went wrong and why". Therefore, most syntheses of organic compounds are labor-intensive and demanding. Additionally, most final synthetic routes to desired organic molecules are usually very different from initially planned routes. A highly skilled chemist can agree that for many successful organic compounds made, many failures are encountered and experimental repetition is common. This also

contributes to the burden and unpredictability of the syntheses of said compounds. (see "Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design" 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

(5) Working Examples: Applicant shows examples R1 and R2 being H, tetrahydropyranylalkylcarbonyl, piperidinyl alkylcarbonyl, alkylcarbonyl, phenyloxyalkylcarbonyl, acetyl, phenylalkanoyl, cyclohexylalkylsulfonyl, alkyl, cyclohexylcarbonyl, alkylaminoalkyl, imidazoylalkylphenyl, alkylaminecarbonyl, indenealkylcarbonyl, pyridinylalkylcarbonyl; R3 and R4 being H, alkoxycarbonyl; R5 being H; and R being phenyl substituted with alkoxyalkoxy, and H, but no working examples were shown wherein R1, R2, R3, R4, R5 and R covers the entire scope as claimed.

(6) Skill of those in the art: The ordinary artisan is highly skilled, e.g. a masters or PhD level chemist.

(7) The quantity of experimentation needed: Since there are very limited working examples as described above, the amount of experimentation is expected to be high and burdensome.

Due to the level of unpredictability in the art, the very limited guidance provide, and the lack of working examples, the Applicant has not provided sufficient guidance for the artisan to make the invention.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claims 6-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims: Treatment or prevention of hypertension, heart failure, glaucoma, cardiac infraction, kidney failure and/or restenosis using highly substituted amino alcohol compounds and pharmaceutical compositions of Formula I.

(2) The nature of the invention: The invention is the method of using highly substituted amino alcohol compounds and pharmaceutical compositions of Formula I to treat or prevent hypertension, heart failure, glaucoma, cardiac infraction, kidney failure and/or

restenosis.

(3) Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(4) Direction or Guidance: The Applicant does not show or demonstrate the use compounds and pharmaceutical compositions of Formula I towards treatment or prevention of hypertension, heart failure, glaucoma, cardiac infraction, kidney failure and/or restenosis. The Specification does not show any biological data pertaining to the outcome of these assays, in vitro or in vivo experiments using claimed compounds. There is no direction or guidance as how to hypertension, heart failure, glaucoma, cardiac infraction, kidney failure and/or restenosis using compounds and pharmaceutical compositions of Formula I.

(5) State of the Prior Art: Treatment and prevention of pain and inflammation is not well developed and is highly unpredictable. The state of the prior art for their treatments involve screening, *in vitro* and *in vivo,* that provides data to determine if compounds exhibit the desired claimed activities. The Applicant has not provided any art recognized evidence that shows the use of compounds and compositions claimed for the prevention and/or treatment of hypertension, heart failure, glaucoma, cardiac

infraction, kidney failure and/or restenosis.

(6) Working Examples: The Applicant has provided no working examples. Nor has Applicant directed the skilled artisan to disclosures in the art that may be used to extrapolate the intended use of the compounds and compositions for the prevention and/or treatment of hypertension, heart failure, glaucoma, cardiac infraction, kidney failure and/or restenosis.

(7) Skill of those in the art: The ordinary artisan is highly skilled such as a medical doctor, doctor of philosophy in science, a nurse practitioner, etc.

(8) The quantity of experimentation needed: In the absence of working examples, which provide sufficient representative disclosures necessary to provide enablement for the treatment and prevention of pain and inflammation, undue experimentation would indeed be required to practice the instant invention. The amount of experimentation is expected to be unduly high and burdensome.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

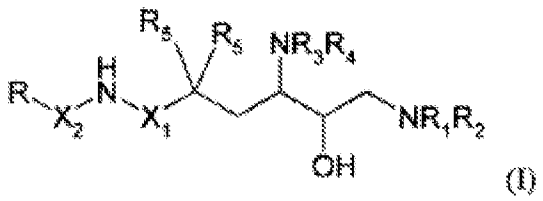
F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 8-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of copending Application No. 2007/0021399 (11/488,858). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following.

US '399 claims the use of compounds of formula I:



(I)

which is the exact same scope of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/John Mabry/
Examiner
Art Unit 1625

/Rita J. Desai/
Primary Examiner, Art Unit 1625